Remarks

Applicants respectfully request consideration of this Amendment and Reply after a Final Office Action because it places the claims in condition for allowance or in better form for consideration on appeal. *See* 37 C.F.R. § 1.116(b).

Upon entry of the foregoing amendments, claims 1, 3-5, 7-13, 16 and 20 are pending in the application, with claim 1 being the sole independent claim. Claims 2, 6, 14, 15, 17-19, 21 and 22 were previously canceled without prejudice to or disclaimer of the subject matter therein. Claim 1 is sought to be amended to further clarify the subject matter of the present invention. Support for the amendment of claim 1 can be found, for example, at page 4, lines 5-14 and Examples 1-7 of corresponding Int'l Pub. No. WO 00/27997 and original claim 7. In addition, the dependency and/or antecedent basis of claims 3-5 and 7-13 have been amended in view of the amendment of claim 1. Accordingly, these changes do not add any new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Rejections Under 35 U.S.C. § 112, First Paragraph

A. Written Description / New Matter

The Examiner maintains the rejection of claims 1, 3-5, 7-13, 16 and 20 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement (new matter). *See* Office Action at page 2. Specifically, the Examiner

alleges that support is not provided in the specification for the breadth of the term "pyruvate" in the claims. *See* Office Action at page 2. Applicants respectfully disagree with the Examiner's position.

The test for the written description requirement is whether, at the time of filing, one skilled in the art could have reasonably concluded that the inventor had possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); *see also* M.P.E.P. § 2163.02. An important consideration in assessing written description of a claimed invention is the knowledge of one skilled in the art. *See Capon v. Eshhar*, 418 F.3d 1349, 1357-1358 (Fed. Cir. 2005)("[t]he descriptive text needed to meet these [written description] requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence."). Moreover, the disclosure of a single species has also been found to be sufficient to support a claimed genus when the disclosure of that species would lead a person of ordinary skill to the genus. *See In re Herschler*, 591 F.2d 693 (CCPA 1979); *see also* M.P.E.P. § 2163.05. In *Herschler,* the Court held that the disclosure of one corticosteroid was sufficient to support "physiologically active steroid" because the use of the compound would lead one of ordinary skill to the entire class of compounds. *Id.* at 697.

Furthermore, *in haec verba* support is not necessitated by the written description requirement of 35 U.S.C. § 112, first paragraph. *See Union Oil of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 1000 (Fed. Cir. 2000); *see also* M.P.E.P. § 2163.02 ("The subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba* in order for the disclosure to satisfy the description requirement."). Newly

added claim limitations may be supported in the specification through express, implicit, or inherent disclosure. *See* M.P.E.P. § 2163(I)(B) and § 2163.07(a).

Applicants assert that the specification provides adequate written description support under 35 U.S.C. § 112, first paragraph, for the breadth of "pyruvate" encompassed by the presently-pending claims. Specifically, the specification provides general disclosure for methods of culturing cells (*see, e.g.,* lines 5-7, page 1 of the specification), as well as multiple specific examples of culture media containing sodium pyruvate (*see, e.g.*, Table 1). In view of Federal Circuit precedent, this disclosure would lead the person of ordinary skill in the art to the full breadth of the term "pyruvate," in particular, upon consideration of the knowledge of one of ordinary skill in the art at the time the present application was filed.

At the time the present application was filed, one of ordinary skill in the art would have understood that glucose was the primary energy source of most organisms. *See, e.g.*, Lehninger *et al.*, eds., Principles of Biochemistry, 2nd ed., New York, NY, Worth Publishers, Inc.; 1993; pages 400-401; attached as Exhibit A. Energy was known to have been predominantly derived from glucose by glycolysis, the process whereby glucose is converted to pyruvate, which then produces ATP for cells. *See id.* at page 401. As such, at the time the present application was filed, culture medium was often supplemented with pyruvate to provide cells with easy access to the components for energy production. *See id.* and Brinster and Troike, *J. Anim. Sci. 49 Suppl 2*: 26-34; 1979; abstract attached as Exhibit B. Several different salts of pyruvate were also known in the art at the time the present application was filed including, for example, sodium pyruvate, potassium pyruvate (Ogawa *et al.*, *J. Urol. 135*: 1057-1060; 1986; abstract

attached as Exhibit C), calcium pyruvate (Ivy *et al., Am. J. Clin. Nutr. 59*: 331-337; 1994; attached as Exhibit D), and ammonium pyruvate (Ježek and Borecký, *Am. J. Physiol. 275*: C496-C504; 1998; attached as Exhibit E). Therefore, at the time the present application was filed, one of ordinary skill in the art would know that pyruvate was routinely added to cell culture medium as an energy source, and would know several exemplary salts of pyruvate. Accordingly, one of ordinary skill in the art would implicitly understand from the disclosure of sodium pyruvate in a cell culture medium that pyruvate was the essential component for cellular energy production and that other pyruvate salts could clearly be used in such medium.

Thus, the specification provides adequate written descriptive support under 35 U.S.C. § 112, first paragraph, for the presently-pending claims. Accordingly, Applicants respectfully request that the rejection be reconsidered and that it be withdrawn.

The above notwithstanding, Applicants note that claim 16 specifies that the pyruvate is "sodium pyruvate." As such, it is Applicants' understanding that at least claim 16 falls within the scope of subject matter that the Examiner finds supported by the disclosure. *See, e.g.*, Office Action at page 2.

B. Enablement

The Examiner maintains the rejection of claims 1, 3-5, 7-13, 16 and 20 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. *See* Office Action at pages 3-6. In particular, the Examiner maintains that the state of the art at the time the present application was filed teaches that various factors affect the production of recombinant proteins in serum-free medium. *See* Office

Action at page 3. The Examiner indicates that "[t]he specification does not enable culturing cells expressing recombinant human EPO using Culture Medium 3 alone ...," and is "limited to sequential culture conditions that sustain the growth and proliferation of CHO cells to produce EPO." Office Action at page 5. Applicants respectfully disagree for at least the reasons of record.

However, solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended independent claim 1 to specify a method for obtaining human erythropoietin comprising culturing and expanding mammalian cells which express recombinant human erythropoietin in culture medium comprising serum; culturing the cells in culture medium consisting of: (i) DMEM; (ii) F12 medium; (iii) insulin; and (iv) $NaHCO_3$, glucose, lactose, galactose, ethanolamine, pyruvate, glutamine, tryptophan, asparagine, and serine as additives; separating supernatant containing human erythropoietin from the cells; and concentrating the supernatant and recovering human erythropoietin.

In view of the Examiner's comments, for example, at page 4 of the Office Action, it is Applicants' understanding that the amended claims fall within the scope of subject matter that the Examiner finds enabled by the specification. However, Applicants will address the Examiner's arguments in the event that the Examiner may find them applicable to the amended claims.

As a preliminary matter, the Examiner cites Wang *et al.* (2002), Yang *et al.* (2002), Schröder *et al.* (2004), and Lee *et al.* (1999) at pages 3 and 4 of the Office Action as evidence that the state of the art at the time of filing teaches various factors affect the production of recombinant proteins in serum-free medium. Applicants note

that these references were published after the November 6, 1998 priority date of the present application, as currently claimed. According to M.P.E.P. § 2164.05(a), "[p]ublications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing." *See also In re Budnick*, 537 F.2d 535, 538 (CCPA 1976)(In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of an enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). Applicants submit that the cited references cannot be properly relied upon as evidence of the state of the art at the time of filing of the present application, based on the current record.

The above notwithstanding, a person of ordinary skill in the art could practice the subject matter of the amended claims without undue experimentation, based on the guidance in the specification and the level of skill in the art. Undue experimentation does not mean "no" experimentation, only that it be reasonable. *See, e.g., In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)("The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."). In contrast to the Examiner's assertion, it is clear the state of the art is such that recombinant proteins can be successfully produced in cells grown in serum-free medium without undue experimentation.

The references cited by the Examiner, Wang *et al.*, Yang *et al.*, Schröder *et al.*, and Lee *et al.*, teach a variety of serum-free media to produce recombinant EPO (rEPO)

from cultured cells, and teach that the ordinary artisan can adapt a cell line to grow in serum-free medium and achieve production of the recombinant protein. For example, "[o]nly minor changes in the medium formulation were necessary for its use in the cultivation of anchorage-dependent and suspension cells. Adaptation of cells grown in the [serum-free] formulation to a protein free medium was easy and straight forward." Schröder *et al.* at page 290. As such, Schröder *et al.* clearly teach that optimizing a cell culture medium formulation to grow cells in serum-free medium is well within the skill of the ordinary artisan and would not require undue experimentation.

Here, amended claim 1 provides a specific list of cell lines for the production of rEPO, a list of specific additives for the DMEM and F12 medium for the production of rEPO from these cells, and specific steps for culturing and expanding these cells, separating and concentrating supernatant from these cells, and recovering rEPO from the supernatant. Thus, the only thing remaining for the ordinary artisan is determining the concentration of additives. Determining the concentration of additives for a medium for the production of a recombinant protein by culture can easily be achieved, for example, by statistical optimizations based on the Placket-Burman design. *See, e.g.,* Lee *et al.* at Abstract. According to Schröder *et al.*, the production of a protein-free medium is achieved by the removal or addition of individual components followed by observing the growth of the cells. *See, e.g.*, Schröder *et al.* at pages 288-290. As pointed out by Schröder *et al.* and Lee *et al.*, these optimization techniques would not require ingenuity beyond those of the ordinary laboratory worker, especially when the laboratory worker is already given the specific additives to include in the medium. *See, e.g.*, Schröder *et al.* at page 290, and Lee *et al.* at page 92.

At page 5 of the Office Action, the Examiner alleges that "[t]he specification fails to correlate the culture conditions obtained with CHO cells to COS, BHK, Namalwa and HeLa cells," and that it is unclear that serum-free conditions would allow COS, BHK, Namalwa and HeLa cells to express rEPO. Applicants respectfully disagree.

According to the specification, the rEPO-expressing cells of the invention are not limited to CHO cells, and can be selected from mammalian cells, or in some embodiments, from CHO, COS, BHK, Namalwa or HeLa cells. *See, e.g.*, page 5, lines 24-27 of the specification. Also, at the time the present application was filed, one of ordinary skill in the art would have understood that COS, BHK, Namalwa and HeLa cells could be utilized to express recombinant proteins in serum-free conditions, and would know methods to express recombinant proteins in these cells under such conditions. For example, Lévesque *et al.* (*Biotechniques 11*:313-318; 1991; abstract attached as Exhibit F) report a defined medium that allows efficient DNA transfections and recombinant protein production in COS cells cultured in serum-free conditions. Hill *et al.* (*J. Lipid Res. 34*: 1245-1251; 1993; attached as Exhibit G) report the establishment of a BHK cell line that efficiently expresses large quantities of recombinant lecithin:cholesterol acyltransferase in serum-free medium. Miyaji *et al.* (*Cytotechnol. 4*:39-43; 1990; abstract attached as Exhibit H) report that the Namalwa cell line, KJM-1, can be utilized to express foreign genes, such as human beta-interferon and human lymphotoxin, in serum-free medium. In addition, Rindisbacher *et al.* (*J. Biol. Chem. 270*: 14220-14228; 1995; attached as Exhibit I) describe that infection of HeLa cells with vaccinia virus containing the extracellular domain of the human polymeric immunoglobulin receptor results in high-efficiency secretion of human secretory

component (hSC) in serum-free medium. In view of the disclosure of the specification and the knowledge of one of ordinary skill in the art, it is clear that COS, BHK, Namalwa and HeLa cells can be used to express foreign polypeptides, such as rEPO, in serum-free conditions. As such, one of ordinary skill in the art could correlate the specific examples of the specification involving CHO cells to at least COS, BHK, Namalwa and HeLa cells.

For at least these reasons, the teaching in the art in conjunction with the Examples provided in the specification indicate that a person of ordinary skill in the art at the time of filing would have possessed the knowledge and skills necessary to make and use the subject matter of the present claims. Thus, any experimentation required to practice the claimed methods would have been reasonable, not undue.

II. Rejection Under 35 U.S.C. § 112, Second Paragraph

Applicants thank the Examiner for withdrawing the prior rejection of claims 1, 3-5, 7-13, 16 and 20. *See* Office Action at page 7.

III. Double Patenting

The Examiner maintains the rejection of claims 1, 3-5, 7-13, 16 and 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 7-13 of U.S. Patent No. 6,777,205. *See* Office Action at page 7. Applicants respectfully disagree with the Examiner's assertion. However, solely to advance prosecution, Applicants will submit a terminal disclaimer in accordance with 37 C.F.R. § 1.321(c) upon the notification by the Examiner of allowable subject matter.

IV. Second Supplemental Information Disclosure Statement

Applicants thank the Examiner for considering the documents cited in the Information Disclosure Statement filed on November 6, 2001 and the First Supplemental Information Disclosure Statement filed on April 21, 2005. However, it appears that the Examiner has not provided initialed copies of Form PTO/SB/08A and Form PTO/SB/08B accompanying the Second Information Disclosure Statement filed on September 21, 2007. Applicants respectfully request that the Examiner initial the documents cited on these Forms and return a copy of the initialed Forms to Applicants.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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